REMARKS

Claims 1-35 are pending in the application. Claims 1 and 31 have been amended. No new matter has been added. Reconsideration of the claims is respectfully requested.

Claims 1-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Carlyle et al. (99/37337), hereinafter referred to as the "Carlyle application", in view of Semenza et al. (6,124,131), hereinafter referred to as the "Semenza patent", or Tsuzuki et al. (Cancer Research. 60. 2000), hereinafter referred to as the "Tsuzuki article".

Amended claim 1 specifies a medical device comprising a stimulation compound associated with the medical device. The stimulation compound stimulates production of VEGF and the medical device can be an implantable medical device, a catheter, a dressing, or a surgical instrument.

Similarly, claim 31 specifies a method of producing a medical device by associating a stimulation compound with a biocompatible material to stimulate production of growth factors.

The Examiner states the Carlyle application teaches coating medical devices with VEGF for the effects produced, and further alleges it would have been obvious at the time the invention was made to substitute HIF-1 alpha for the VEGF because the prior art teaches that HIF-1 alpha stimulates *in vivo* production of the desired compound VEGF. According to the Examiner on Page 3 of the Office Action:

"The reference teaches all of the claimed limitations except that the

> reference uses VEGF and does not teach using a VEGF stimulation compound however at the time the invention was made it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a known VEGF stimulation compound for the VEGF used by Carlyle because such a compound would cause the production of the desired compound VEGF. Applicant does not seem to dispute that HIF-1 alpha is a known stimulator of VEGF production."

Applicants respectfully disagree with the Examiner's reading of the prior art and the Examiner's characterization of HIF-1 alpha for several reasons.

The Carlyle application teaches the use of VEGF and VEGF related compounds in association with prostheses to stimulate chemotaxis and cell growth (See Page 8, lines 4-14 of the Carlyle application, for example). However, the Carlyle application does not disclose or teach the use of a stimulation compound associated with a medical device to stimulate growth factors, as claimed in pending claims 1-35. The Carlyle application does not teach or disclose use of a stimulation compound to stimulate production of a growth factor. Further, the Carlyle application does not disclose a stimulation compound, such as HIF1α, to stimulate production of VEGF. Since the Carlyle application fails to teach or disclose all the claim limitations, the Carlyle application does not render obvious pending claims 1-35.

Next, the Examiner alleges that the Semenza patent and the Tsuzuki article teach that HIF1α can be substituted for the VEGF disclosed in the Carlyle application to stimulate production of VEGF. Neither the Semenza patent nor the Tsuzuki article, either singly or in combination with the Carlyle application, teach or suggest that associating a stimulation compound, like HIF-1α, with a medical device stimulates

production of VEGF (claim 1) or stimulates production of growth factors (claim 31).

The Semenza patent discloses at column 2, lines 25-30 that the genes activated by hypoxia-induced HIF-1 expression in cells include EPO, VEGF, heme oxygenase-1, inducible nitric oxide synthase, and glycolytic enzymes aldolase A, enolase 1, lactate dehydrogenase A, phosphofructokinase I, and phosphoglycerate kinase I. Furthermore, HIF-1 protein concentration increases exponentially as cells are subjected to decreasing O_2 concentrations. (See Column 2, lines 29 to 34). Therefore, the Semenza patent discloses induction of HIF-1 protein in response to hypoxic or non-hypoxic conditions. In contrast, the stimulation compound is associated with the medical device of the above-identified application rather than being produced and measured in the cell line. Therefore, the combination of the Carlyle application in view of the Semenza patent is incorrect since the HIF-1 protein of the prior art is induced and not associated with a medical device.

The Examiner alleges HIF-1α stimulates the *in vivo* production of VEGF, and fails to mention that the Semenza patent discloses the observed HIF-1α expression is the result of *in vivo* stimulation via hypoxic or non-hypoxic conditions. Furthermore, this induction of HIF-1α activity documented in the prior art is not the same as associating HIF-1α as part of a cell line. Therefore, the Carlyle application in view of the Semenza patent do not teach or render obvious the present invention as defined in claims 1-35.

As noted, in establishing a case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally

available to one of ordinary skill in the art, to modify the references. There is no suggestion in the prior art to associate a stimulation compound like HIF-1 protein with a medical device to produce growth factors like VEGF. Furthermore, the Examiner has not provided any evidence that demonstrates inclusion or association of HIF-1 protein as part of a cell line stimulates VEGF production. Nevertheless, should the Examiner possess evidentiary support, Applicants respectfully request the Examiner provide documentary evidence. See MPEP §2144.03.

The Examiner also relied on the Tsuzuki article to allege that substitution of HIF-1 for VEGF in the Carlyle application would have been an obvious modification. The Tsuzuki article discloses the results of induced HIF1α on VEGF production rather than what occurs when HIF1α is associated with a medical device.

As discussed, the present invention discloses associating stimulation compounds like HIF-1 to medical devices to stimulate production of VEGF or other growth factors, rather than inducing *in vivo* HIF-1 expression to stimulate VEGF production. Therefore, the use of a stimulation compound to stimulate production of a growth factor when the stimulation compound is associated with a medical device is not obvious in light of the prior art. As a result, the rejection of claims 1-35 based on the combination of the Carlyle patent in view of the Semenza patent or the Tsuzuki article is incorrect.

In view of the above remarks, Applicants respectfully request withdrawal of the rejection of claims 1-35 under 35 U.S.C. 103(a) as being obvious over the Carlyle

application in view of the Semenza patent or the Tsuzuki article.

In view of the amendments and reasons provided above, it is believed that all pending claims are in condition for allowance. Applicants respectfully request favorable reconsideration and early allowance of all pending claims.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicant's attorney of record, Hallie A. Finucane at 612-333-3222.

The Director is authorized to charge any fee deficiency required by this paper or credit any overpayment to Deposit Account No. 23-1123.

Respectfully submitted,

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